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**Case Reporte**

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# Renal carcinoma associated with end-stage kidney disease: A case series from a tertiary Portuguese hospital

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**Abstract.** *End-stage kidney disease (ESKD) is associated with a higher incidence of renal cell carcinoma (RCC). Here we report a case series of 56 patients with ESKD who underwent radical nephrectomy for suspected renal masses at a tertiary hospital in Portugal from January 2017 to January 2024. Patient records were reviewed retrospectively to collect clinical, surgical, and pathological data. Among these patients, 12 had benign tumors, while 44 were diagnosed with malignant tumors, accounting for approximately 78.5% of the cohort. The histological analysis revealed the following distribution: clear cell RCC (20 cases, 45%), papillary RCC (11 cases, 25%), ACKD-associated RCC (6 cases, 14%), clear cell papillary RCC (4 cases, 9%), and chromophobe RCC (3 cases, 7%). Notably, the majority of patients (95.5%) had stage I malignant tumors, yet the prognosis for patients with ESKD was poorer compared to non-ESKD patients, with 7 patients succumbing during the follow-up period.*

*This study underscores the complex relationship between ESKD and RCC, highlighting the challenges in diagnosis and management. Despite regular monitoring leading to early detection of tumors, the overall prognosis remains adversely affected by the compromised immune status and comorbid conditions prevalent in this population. The findings call for enhanced surveillance and personalized management strategies for RCC in patients with ESKD.*

**Keywords:** *end-stage kidney disease, renal cell carcinoma, acquired cystic kidney disease, hemodialysis, pathology.*

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# Карцинома нирки, асоційована з термінальною стадією хронічної хвороби нирок: серія клінічних випадків із високоспеціалізованої лікарні Португалії

Клініка Сан-Хосе, Центральна Лісабонська лікарня та університетський центр, Лісабон, Португалія

**Резюме.** *Термінальна стадія хронічної хвороби нирок (ХХН ВД) асоційована з високою частотою нирково-клітинної карциноми (НКК). У цій роботі ми повідомляємо про серію випадків із 56 пацієнтів з ХХН ВД, які перенесли радикальну нефректомію з приводу підозри на новоутворення в нирках у високоспеціалізованій лікарні Португалії з січня 2017 по січень 2024. Записи пацієнтів були ретроспективно переглянуті для збору клінічних, хірургічних і патологічних даних. Серед включених пацієнтів 12 мали доброякісні пухлини, тоді як у 44 були діагностовані злоякісні пухлини, що становило 78,5% когорти. Гістологічний аналіз виявив таку структуру випадків: світлоклітинна карцинома нирки (20 випадків, 45%), папілярна карцинома нирки (11 випадків, 25%), карцинома нирки, асоційована з набутим кістозним захворюванням нирок (6 випадків, 14%), світлоклітинна папілярна карцинома нирки (4 випадки, 9%) та хромофобна карцинома нирки (3 випадки, 7%). Примітно, що більшість пацієнтів (95,5%) мали злоякісні пухлини I стадії, але прогноз був гіршим порівняно з пацієнтами без ХХН ВД: 7 пацієнтів померли протягом періоду спостереження.*

*Наше дослідження підкреслює складний зв'язок між ХХН ВД та НКК, висвітлюючи проблеми в діагностиці та лікуванні. Незважаючи на регулярний моніторинг, результатом якого є рання діагностика новоутворення, загальний прогноз залишається несприятливим через імунодефіцит і супутні захворювання, поширені в цій популяції. Отримані результати вимагають посиленого спостереження та персоналізованих стратегій лікування НКК у пацієнтів із ХХН ВД.*

**Ключові слова:** *термінальна стадія хронічної хвороби нирок, нирково-клітинний рак, набута кістозна хвороба нирок, гемодіаліз, патологія.*

**Introduction.** Chronic kidney disease (CKD) is a progressive condition marked by a gradual decline in kidney function over time. It involves various pathophysiologic processes that lead to impaired kidney function and a reduced glomerular filtration rate. In advanced stages, CKD can progress to end-stage kidney disease (ESKD), where kidneys fail to perform essential functions, resulting in the accumulation of toxins, fluids, and electrolytes in the body. This uremic syndrome requires renal replacement therapy, typically through dialysis or kidney transplantation, to sustain life [1, 2].

ESKD is a growing public health concern, affecting millions globally. The prevalence of ESKD has risen due to increased incidences of diabetes and hypertension, both primary risk factors for CKD. ESKD patients encounter numerous complications, including elevated risks of cardiovascular disease, infections, and various malignancies, such as renal cell carcinoma (RCC) [3].

RCC is the most common kidney cancer, accounting for approximately 85% of kidney malignancies. ESKD patients, particularly those with acquired cystic kidney disease (ACKD), are at a significantly higher risk of RCC. The likelihood of RCC in patients with ACKD, a condition marked by multiple kidney cysts from long-term dialysis, is estimated to be 3–24 times higher than in the general population [4–6].

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The development of RCC in ESKD patients is multifaceted, with chronic inflammation, oxidative stress, and genetic mutations playing critical roles. Long-term dialysis contributes to toxin and free radical buildup, leading to chronic inflammation and oxidative stress, which can damage cellular DNA and promote oncogenesis. Genetic mutations, such as changes in the von Hippel-Lindau (VHL) gene, may also be exacerbated by chronic oxidative stress and inflammation in ESKD patients [6–8].

Advances in RCC classification have highlighted distinct subtypes of RCC in ESKD patients. The 2016 World Health Organization (WHO) classification introduced new RCC subtypes, including acquired cystic disease-associated RCC (ACD-associated RCC) and clear cell papillary RCC (CCP-RCC), which have unique histological and clinical profiles and are particularly relevant to ESKD patients [9].

This case series study describes the clinical and histopathological characteristics of renal tumors in native kidneys of ESKD patients treated at a tertiary Portuguese hospital.

**Case series**. A total of 56 ESKD patients who underwent radical nephrectomy for suspected renal masses

at a tertiary Portuguese hospital between January 2017 and January 2024 were included in this report. Patient records were reviewed retrospectively to gather clinical, surgical, and pathological data, focusing on RCC types and their association with long-term dialysis. The hospital's Institutional Review Board approved the study, waiving informed consent due to its retrospective nature. Patient confidentiality was maintained, with all data anonymized per the Declaration of Helsinki and local ethical guidelines.

Of these patients, 12 had benign tumors, including multilocular cystic renal neoplasm, acquired cystic kidney disease (ACKD), and oncocytomas. Malignant tumors were found in 44 patients, accounting for approximately 78.5% of those who underwent surgery. The histological types included clear cell RCC (20 cases, 45%), papillary RCC (11 cases, 25%), ACKD-associated RCC (6 cases, 14%), clear cell papillary RCC (4 cases, 9%), and chromophobe RCC (3 cases, 7%) (Fig. 1).

The majority of malignant tumors were classified as stage I (42 cases), with one case each of stages II and III. The median follow-up period was 40.4 months, during which 7 deaths were recorded. The median age of ESKD patients with malignant tumors was 60 years (IQR 47–73), with a male-to-female ratio of 1.59. Detailed patient and pathological characteristics are shown in Table 1.

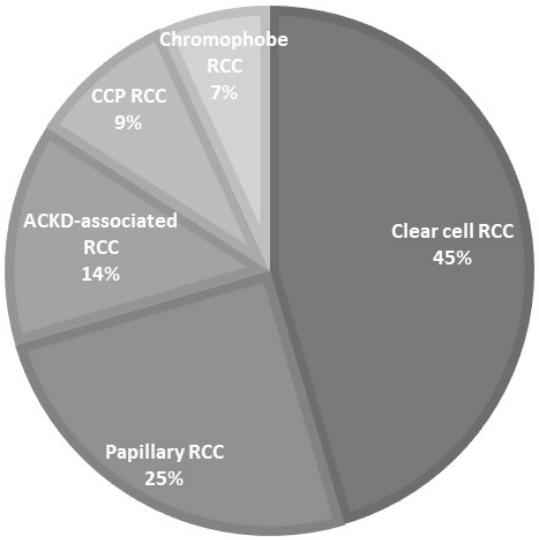


Fig. 1. Distribution of histological subtypes of RCCs in patients with ESKD from our study.

*Table 1*

**Clinical and pathological features of patients with ESKD and renal tumors**

| | | |
|---|---|---|
| No. of patients | | 44 |
| Age, years (range) | | 60 [IQR 47-73] (45-94) |
| Sex (%) | Male | 27 (61) |
| | Female | 17 (39) |
| ECOG Performance Status (%) | 0 | 26 (59) |
| | 1 | 16 (36) |
| | ≥2 | 2 (5) |
| Etiology of ESKD (%) | Diabetes Mellitus | 6 (14) |
| | Hypertension | 12 (27) |
| | Nephrotic Conditions | 3 (7) |
| | Focal Segmental Glomerulosclerosis | 2 |
| | Membranous Nephropathy | 1 |
| | Nephritic Conditions | 13 (29) |
| | Chronic Glomerulonephritis | 3 |
| | Lupus Nephritis | 3 |
| | IgA Nephropathy | 1 |
| | Membranoproliferative glomerulonephritis | 1 |
| | Wegener's Granulomatosis | 1 |
| | Hemolytic Uremic Syndrome | 4 |
| | Polycystic Kidney Disease | 4 (9) |
| | Unknown/Unclear Causes | 6 (14) |
| Median duration from the onset of renal replacement therapy to tumor diagnosis, years | | 14 [IQR 11] |
| Duration of dialysis, years (%) | <10 | 18 (41) |
| | ≥10 | 26 (59) |
| Median tumor size, cm (range) | | 3,5 (0,5-16) |

*Continuation of Table 1*

| | | |
|---|---|---|
| Pathological stage (%) | stage I | 42 (96) |
| | stage II | 1 (2) |
| | stage III | 1 (2) |
| pT (%) | p1a | 31 (71) |
| | p1b | 11 (25) |
| | p2a | 0 (0) |
| | p2b | 1 (2) |
| | p3a | 1 (2) |
| | p3b | 0 (0) |
| Histology (%) | Clear cell RCC | 20 (45) |
| | Papillary RCC | 11 (25) |
| | ACKD-associated RCC | 6 (14) |
| | CCP RCC | 4 (9) |
| | Chromophobe RCC | 3 (7) |
| Median follow-up, months | | 40.4 [IQR 18] |

The median duration from the onset of renal replacement therapy to tumor diagnosis was 14 years (IQR 11). Figure 2 shows the RCC subtype distribution relative to dialysis duration. Immunosuppressive therapy did not appear to significantly influence RCC development in post-transplant patients.

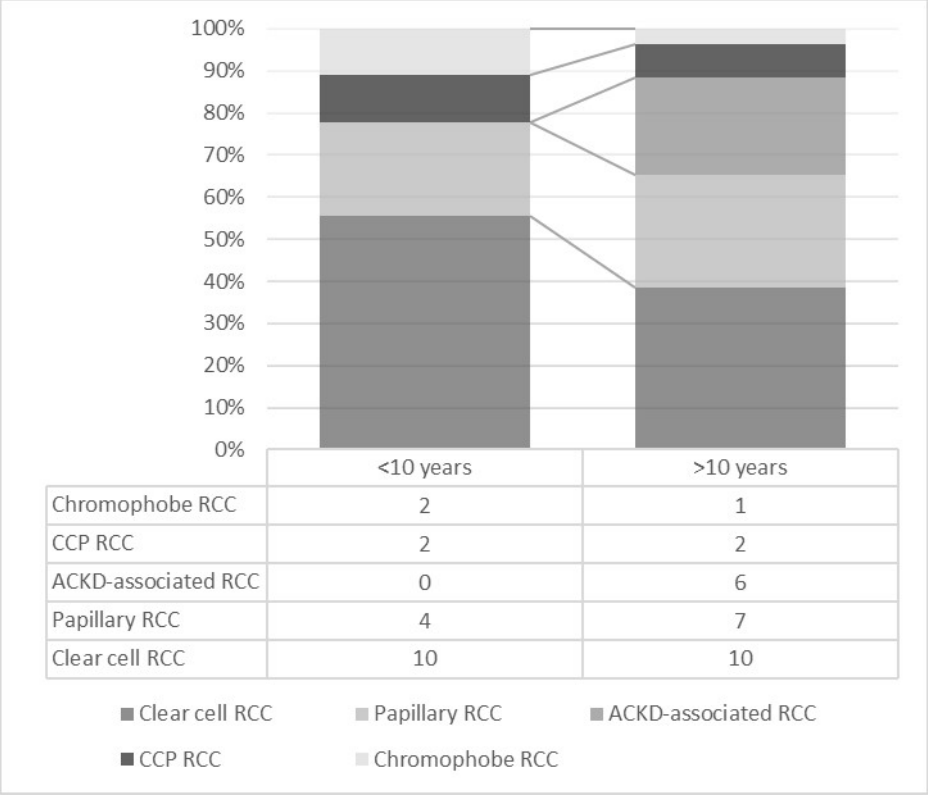


Fig. 2. Distribution of histological subtypes of RCCs in patients with ESKD according to dialysis duration

**Discussion.** The relationship between ESKD and RCC is multifaceted, involving both the underlying pathophysiological changes associated with chronic kidney disease and the effects of long-term renal replacement therapy. The incidence of RCC in patients with ESKD is significantly higher than in the general population, and this increased risk is particularly pronounced in patients with ACKD. ACKD is characterized by the development of multiple cysts in the kidneys, which can undergo malignant transformation over time. The pathogenesis of RCC in ESKD patients is thought to be driven by several factors, including chronic inflammation, oxidative stress, and genetic mutations [**6, 10, 11**].

Chronic inflammation in ESKD patients is a well-documented phenomenon, resulting from the accumulation of uremic toxins and the presence of dialysis-related factors. This chronic inflammatory state can lead to cellular damage and promote oncogenesis. Oxidative stress, which is elevated in ESKD patients due to impaired renal function and dialysis, further contributes to DNA damage and the development of RCC. Additionally, genetic mutations commonly observed in RCC, such as alterations in the von Hippel-Lindau (VHL) gene, can be exacerbated by the chronic oxidative stress and inflammation present in ESKD [4, 7].

Recent classifications by the World Health Organization (WHO) have identified new subtypes of RCC that are particularly relevant to ESKD patients, including ACKD-associated RCC and clear cell papillary RCC (CCP-RCC). ACKD-associated RCC is almost exclusively found in patients who have undergone long-term hemodialysis, as we also observed in our data. Histologically, these tumors exhibit a cribriform or sieve-like architecture, with abundant eosinophilic cytoplasm and large nuclei with prominent nucleoli. The presence of calcium oxalate crystals is a distinctive feature of ACKD-associated RCC, aiding in its diagnosis. CCP-RCC, on the other hand, is characterized by its clear cells and papillary architecture, and it is typically associated with a less aggressive clinical course [12-14].

Patients with ESKD who develop RCC often present with smaller, less aggressive tumors compared to the general population. This can be attributed to the frequent monitoring and imaging that ESKD patients undergo as part of their routine care. However, despite the typically indolent nature of these tumors, the overall prognosis for ESKD patients with RCC is poorer compared to non-ESKD patients. This is due to several factors, including the compromised immune status of ESKD patients, which can hinder the body's ability to mount an effective anti-tumor response, and the presence of other comorbidities that complicate treatment [15, 16]. This was evident in our study, where the vast majority (95.5%) of patients had stage I malignant tumors due to regular monitoring, yet 7 patients died during the follow-up period.

The management of RCC in ESKD patients requires careful consideration of their overall health status and the risks associated with surgery. Nephrectomy remains the primary treatment for localized RCC. However, the decision to proceed with surgery must balance the potential benefits of tumor removal with the risks posed by the patient's compromised renal function and overall health. The risk of RCC recurrence in ESKD patients is influenced by several factors, including tumor stage, histological subtype, and the patient's overall health. Studies have shown that while the stage-specific recurrence-free survival for ESKD-RCC patients is similar to that of non-ESKD patients, cancer-specific and overall survival rates are significantly lower. This underscores the need for vigilant follow-up and monitoring in this high-risk population. Regular imaging and clinical evaluations are essential to detect recurrences early and to manage them promptly [6].

The immune system of ESKD patients is often compromised due to both the disease itself and the immunosuppressive therapy used in patients with kidney transplants. This immunosuppression can facilitate the development and progression of RCC by allowing tumor cells to evade immune surveillance. Furthermore, metabolic disturbances common in ESKD, such as hyperparathyroidism and altered calcium-phosphate metabolism, can contribute to the pathogenesis of RCC [5, 11].

Further research is needed to better understand the unique characteristics of RCC in ESKD patients and to develop targeted therapies that address the specific needs of this population. Advances in molecular and genetic profiling of tumors may lead to more personalized treatment approaches, improving outcomes for ESKD patients with RCC. Additionally, the potential role of novel immunotherapies and targeted therapies in the treatment of ESKD-RCC warrants exploration, given the unique immunological environment in these patients.

**Conclusions.** RCC in ESKD patients presents unique challenges and requires a multidisciplinary approach for optimal management. The increasing incidence of RCC in this population highlights the importance of regular screening and early detection, as well as the need for tailored treatment strategies that consider the patient's overall health. By improving our understanding of the underlying mechanisms and risk factors associated with RCC in ESKD, we can develop more effective interventions and improve the prognosis for these patients.

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**Data availability statement.** The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

**The authors' contributions.**

***João Guerra:*** conceptualization and study design, data acquisition, analysis, and interpretation, drafting of the manuscript, and critical review;

***Vanessa Andrade:*** conceptualization and study design, drafting of the manuscript, and critical review;

***Miguel Brito Lança:*** data acquisition, analysis, and interpretation;

***João Pina:*** drafting of the manuscript, supervision;

***Luís Campos*** Pinheiro: critical review and supervision.

All the authors reviewed the final version of the manuscript and agreed to be accountable for all aspects of the work.

**References:**


1. *Elendu C, Elendu RC, Enyong JM, Ibhiedu JO, Ishola IV, Egbunu EO, et al.* Comprehensive review of current management guidelines of chronic kidney disease. Medicine (Baltimore). 2023;102(23):e33984. doi: 10.1097/MD.0000000000033984.
2. *Mallamaci F, Tripepi G.* Risk Factors of Chronic Kidney Disease Progression: Between Old and New Concepts. J Clin Med. 2024;13(3):678. doi: 10.3390/jcm13030678.
3. *Kompotiatis P, Thongprayoon C, Manohar S, Cheungpasitporn W, Gonzalez Suarez ML, Craici IM, et al.* Association between urologic malignancies and end-stage renal disease: A meta-analysis. Nephrology (Carlton). 2019 ;24(1):65-73. doi: 10.1111/nep.13209.
4. *Hora M, Hes O, Reischig T, Urge T, Klecka J, Ferda J, et al.* Tumours in end-stage kidney. Transplant Proc. 2008;40(10):3354-8. doi: 10.1016/j.transproceed.2008.08.135.
5. *Song C, Hong SH, Chung JS, Byun SS, Kwak C, Jeong CW, et al.* Renal cell carcinoma in end-stage renal disease: Multi-institutional comparative analysis of survival. Int J Urol. 2016;23(6):465-71. doi: 10.1111/iju.13084.
6. Tsuzuki T, Iwata H, Murase Y, Takahara T, Ohashi A. Renal tumors in end-stage renal disease: A comprehensive review. Int J Urol. 2018;25(9):780-786. doi: 10.1111/iju.13759.
7. *Yoshida M, Yao M, Ishikawa I, Kishida T, Nagashima Y, Kondo K,et al.* Somatic von Hippel–Lindau disease gene mutation in clear-cell renal carcinomas associated with end-stage renal disease/acquired cystic disease of the kidney. Genes Chromosom. Cancer 2002; 35: 359–64. doi: 10.1002/gcc.10123.
8. *Kuntz E, Yusenko MV, Nagy A, Kovacs G.* Oligoarray comparative genomic hybridization of renal cell tumors that developed in patients with acquired cystic renal disease. Hum. Pathol. 2010; 41 (9): 1345–9. doi: 10.1016/j.humpath.2009.09.022.
9. *Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM.* The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2016;70(1):93-105. doi: 10.1016/j.eururo.2016.02.029.
10. *Kondo T, Sassa N, Yamada H, Takagi T, Iizuka J, Kobayashi H, et al.* Comparable survival outcome between acquired cystic disease associated renal cell carcinoma and clear cell carcinoma in patients with end-stage renal disease: a multi-institutional central pathology study. Pathology. 2021;53(6):720-727. doi: 10.1016/j.pathol.2021.01.014.
11. *Toyokuni S.* The origin and future of oxidative stress pathology: From the recognition of carcinogenesis as an iron addiction with ferroptosis-resistance to non-thermal plasma therapy. Pathol Int. 2016;66(5):245-59. doi: 10.1111/pin.12396.
12. *Tickoo SK, dePeralta-Venturina MN, Harik LR, Worcester HD, Salama ME, Young AN, et al.* Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. Am J Surg Pathol. 2006;30(2):141-53. doi: 10.1097/01.pas.0000185382.80844.b1.
13. *Nouh MA, Kuroda N, Yamashita M, Hayashida Y, Yano T, Minakuchi J, et al.* Renal cell carcinoma in patients with end-stage renal disease: relationship between histological type and duration of dialysis. BJU Int. 2010;105(5):620-7. doi: 10.1111/j.1464-410X.2009.08817.x.
14. *Sassa N, Hattori R, Tsuzuki T, Watarai Y, Fukatsu A, Katsuno S, et al.* Renal cell carcinomas in haemodialysis patients: does haemodialysis duration influence pathological cell types and prognosis? Nephrol Dial Transplant. 2011;26(5):1677-82. doi: 10.1093/ndt/gfq529.
15. *Klatte T, Seitz C, Waldert M, de Martino M, Kikic Z, Böhmig GA, et al.* Features and outcomes of renal cell carcinoma of native kidneys in renal transplant recipients. BJU Int. 2010;105(9):1260-5. doi: 10.1111/j.1464-410X.2009.08941.x.
16. *Neuzillet Y, Tillou X, Mathieu R, Long JA, Gigante M, Paparel P, et al.* Renal cell carcinoma (RCC) in patients with end-stage renal disease exhibits many favourable clinical, pathologic, and outcome features compared with RCC in the general population. Eur Urol. 2011 ;60(2):366-73. doi: 10.1016/j.eururo.2011.02.035.